REMARKS.

Claims 1-26 are pending. By way of the present amendment, claim 1 has been amended. Claims 22-26 remain pending, but are withdrawn from consideration as a non-elected invention under a restriction requirement.

Support for the amendments to the claims can be found, for example, in the claims as originally filed and at page 4, lines 16-24. The amendments to the claims add no new matter and their entry is respectfully requested. Based on the above amendments and the following remarks, Applicants respectfully requests that the Examiner reconsider the rejections of the claims, that he withdraw same, and that he pass the application to issue.

Applicants acknowledge with appreciation the Examiner's entry of the amendments to the specification to correct inadvertent and obvious typographic mistakes. Applicants further appreciate the Examiner's helpful comments during the interview by telephone on June 9, 1998.

Rejection of claims under 35 U.S.C. §112, second paragraph.

Claims 1-21 are rejected under 35 U.S.C. §112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

Applicants acknowledge with appreciation the Examiner's withdrawal of almost all of the bases of rejection of the claims under 35 U.S.C. §112, second paragraph. The Examiner has, however, maintained rejection of the claims on the grounds that claim 1 is considered vague and indefinite for failing to clearly recite the upper limit of the number of amino acids.

Applicants respectfully traverse this ground of rejection, because the skilled artisan would readily understand the limits of the claims. However, in an effort to expedite the prosecution of this application, the claims have been amended to further clarify what Applicants intend to claim. The Examiner is respectfully requested to withdraw this ground of rejection.

Rejection of the claims under 35 U.S.C. §112, first paragraph.

The claims are rejection under 35 U.S.C. § 112, first paragraph as the claims are considered enabling only for those particular peptides such as the sequences demonstrated to inhibit cytolysis on pages 21 *et seq.* of the specification. Applicants respectfully traverse these rejections based upon the following remarks.

Applicants acknowledge with appreciation the Examiner's withdrawal of six of ten grounds of rejection of the claims under 35 U.S.C. §112, first paragraph. The Examiner has, however, maintained rejection of the claims on four grounds, which will each be addressed in turn.

1. Diverse peptides

The Examiner has maintained the rejection of the claims because the specification allegedly fails to provide an enabling disclosure commensurate in scope with the claims. The Examiner has cited Applicants' teaching that certain peptides inhibit CTL activity and certain ones do not. Specifically for example, the Examiner finds that the ordinary skilled artisan would consider the diversity of peptides as claimed unpredictable and cites the differential activity between HLA-B2702 and HLA-B2705, where the former blocks CTL response, while the latter fails to do so. The Examiner therefore appears to conclude that because of the number of peptides embraced by the claims compared with the number of peptides shown to inhibit CTL activity (or proliferation of lymphocytes) that the skilled artisan would find it necessary to unduly experiment to practice the claimed invention. (Applicants note, that it is unclear to what page the Examiner refers, when he states that "at page 40, lines 1-5", as appears at page 6, paragraph E of the Official Action. Page 40 in the application as originally filed, recites claims 24-26.)

Applicants respectfully traverse this rejection. Applicants appreciate the Examiner's sincere efforts to calculate the number of possible peptide sequences embraced by the claims and the statistical viewing of the claimed invention. However, the presently claimed invention is patentable because Applicants have not only provided a teaching of which amino acid sequences clearly work, some better some not, than others and some which do not inhibit CTL activity, BUT Applicants have also taught the specific number of amino acids that are required for activity AND Applicants have taught convenient assays to determine simply and easily which sequences demonstrate a greater activity than others.

The courts have been quite clear that an applicant is under no duty to provide all details of the mechanism of how an invention works, but rather an applicant is required to provide sufficient guidance so that experimentation can be carried out to practice the claimed invention. The need to conduct routine experimentation does not form the basis for a rejection of the claims under 35 U.S.C. §112, first paragraph. Rather, the question is whether the skilled artisan would be required to conduct undue experimentation that underlies an enablement rejection. The consideration as to whether or not undue experimentation would be required has been set forth by the court in *In re Wands*, 858 F.2d, 731, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants respectfully assert that under these guidelines, only routine experimentation is required to prepare and test any peptide sequence for immunomodulating activity. The Examiner appears to be concerned about the quantity of experimentation required.

When determining the quantity of experimentation necessary, the focus is not on the amount of experimentation necessary to practice the entire genus but rather the amount of experimentation required to practice any particular member. This concept is central to the holding of *In re Wands* where the claims read on the use of any IgM antibody that possessed a particular binding affinity. Clearly, the court recognized that it would require an infinite amount of experimentation to obtain every single possible IgM antibody that could be generated with the

specified affinity. Accordingly, the court focused on the amount of experimentation necessary to practice any particular IgM antibody with the recited binding affinity and not the amount required to practice the entire genus. This focus is further exemplified by the multitude of chemical patents which have issued that contain generic claims reading on tens of thousands of individual members.

The question becomes then how much experimentation is required to (1) prepare a peptide sequence as claimed, (2) test the candidate peptide sequence in one of several assays disclosed for measuring immunomodulating activity, and (3) determine whether the specific peptide sequence results in inhibition of CTL activity or inhibition of cellular proliferation. The Examiner must clearly recognize that Applicants success in preparing the disclosed peptide sequences shows that 1) it is routine to perform these steps for any individual peptide and 2) the success noted by Applicants provides a reasonable basis for predicting success with other peptides sequences. Such reasonable basis does not require absolute certainty for each and every sequence, however. Otherwise, the *Wands* Court would have held that only those disclosed specific antibodies could be claimed. The Court recognized that some inoperative (or less active) embodiments do not defeat all claimed embodiments.

Similarly, Applicants respectfully point out that the claimed peptides are limited to lymphocyte immunomodulating activity. This activity may be greater in some peptides than in others, however, regardless of the degree of activity, as long as such peptides possess immunomodulating activity they are within the ambit of the claims.

2. Variants

The claims are rejected as requiring undue experimentation for reasons similar to those stated by the Examiner concerning "Diverse Peptides" as discussed *supra*. Again, Applicants respectfully maintain that the specification provides clear guidance to the skilled artisan as to the

variations in amino acid sequence; how to screen for activity correlated to the amino acid sequence as well as which amino acids are critical to the immunomodulating activity.

However, in an effort to expedite the prosecution of this application, the claims have been amended to delete the recitation of "variants" and further clarify what Applicants intend to claim. The Examiner is respectfully requested to withdraw this ground of rejection.

3. Immunosuppressive agent

The Examiner has maintained this ground of rejection with regard to claim 18. The Examiner has further indicated that it would be helpful to provide evidence that the recited peptides along would have activity in increasing allograft survival.

Applicants respectfully traverse this ground of rejection for the reasons of record and in view of the following additional comments. The present claim 18 is now limited to a therapeutically effective regimen, which the skilled artisan could easily identify following routine experimentation. Further, Applicants note that in the specification at page 35, lines 17-26, the use of the claimed peptides without an immunosuppressive agent clearly results in an extension of the period of acceptance of a transplant. While, the specification does teach that an improved outcome is expected by using both the claimed peptides and an immunosuppressive agent, there is clear guidance to the ordinary skilled artisan how to extend the period of acceptance of the transplant by using the claimed peptide in a therapeutically effective regimen. The Examiner is respectfully requested to withdraw this ground of rejection.

As a minor point, Applicants' undersigned representative notes that in the amendment filed December 19, 1997, in claim 18, at the end of the first line, the sentence reads: "acceptance by a recipient a", rather than correctly reciting: "acceptance by a recipient of a". Since the amendment merely inadvertently omitted "of" and did not request that "of" be cancelled, it would be appreciated if the Examiner would confirm that the claim continues to correctly recite "recipient of a".

4. Homodimer/Heterodimer

Applicant traverses the Examiner's rejection of the claims as lacking enablement. Applicants respectfully traverse this rejection.

Further, Applicants note that the Examiner pointed out that Table 1, at page 21 of the specification only exemplifies the "beta-alpha" variety and not other dimeric forms. Applicants interpret what the Examiner intends to point out that Table 1 provides peptides of the formula $\alpha\beta$, where α is b and β is a (based upon the claimed formula:

(a) $\{R\ aa^{76\text{-}77}\ L\}\ (aa^{79\text{-}84})$ or (b) $(aa^{84\text{-}79})\ \{L\ aa^{77\text{-}76}\ R\}$).

That is, the Examiner considers that the dimers presented in Table 1 are only of the: (b)/a variety, where b=$(aa^{84\text{-}79})\ \{L\ aa^{77\text{-}76}\ R\}$ and a=$\{R\ aa^{76\text{-}77}\ L\}\ (aa^{79\text{-}84})$.

However, Applicants further note that Table 1, actually provides the following dimer varieties: B2702.84-75/75-84 is actually: b/a; and B2702.84-75/84-75 is actually: b/b

In the specification at page 22, line 9, the a/a dimer (B2702.75-84/75-84) is disclosed as having similar activity. Also, a number of dimers are presented with at least one amino acid substituted from the wildtype sequence.

The Examiner's suggestion that the claims are not enabled by the specification because only one allelic product (HLA-B2702) is taught is considered inaccurate. The Examiner is urged to review Example 2, beginning at page 26, whereat peptides of the B7 allele are also shown as having immunomodulating activity (e.g., see page 28, line 26; Table 4 at page .29; page 30, line 22).

Applicants respectfully urge that the specification clearly provides broader guidance than the Examiner suggested. The skilled artisan in following the specification would not require undue experimentation to identify which sequences possess lymphocyte immunomodulating activity in view of the several assays taught as well as the identification of amino acids critical to

this activity. Applicants therefore request the Examiner to reconsider this ground of rejection and withdraw same.

Rejection of the claims under 35 U.S.C. §103(a).

Claims 1-21 are rejected under 35 U.S.C. § 103(a) as obvious over Olsson (US PN 5,073,540) or WO88/05784.

Each of Olsson and WO88/05784 teach peptide sequences relating to alleles of the MHC Class 1 antigens.

Applicant respectfully traverses this rejection in view of the following remarks. Neither of these references teaches nor suggests the presently claimed dimeric compounds, methods of using or method of genetic expression to make. These references fail to teach the significance of the claimed sequence of amino acids as well as the significance of creating dimers of these sequences, as presently claimed. Neither of the references teaches or suggest the acylation of the N-terminal nor do either of the references teach amidation or esterification of the C-terminal regions.

The Examiner in response notes that "one with ordinary skill in the art would at least expect that dimers of the same unit would exert the same functional effects as a monomer." This is a surprising conclusion, since the Examiner has not pointed to any teaching of the reference or the art for support.

However, Applicants have disclosed that, for example, the "inverted repeat dimer B2702.84-75/75-84 . . . was as potent as B2702.60-84 in terms of concentration required to achieve 50% inhibition of cytolysis . . . and was superior to this peptide in that it completely inhibited cytolysis"(See: the Specification at page 22, lines 5-8). Applicants have noted that the Examiner would drop this rejection if the claims were limited to palindromic dimers, such as B2702.84-75/75-84. Applicants further point out that the B2702.75-84/75-84 is not a

palindromic dimer, but yet it showed similar activity to the palindrome (See: the Specification at page 22, lines 8-9).

Applicants respectfully urge that neither alone nor together do Olsson and WO88/05784 teach or suggest the presently claimed compounds.

Applicant respectfully submits that these rejections may be properly withdrawn and the claims found allowable. If the Examiner considers that a telephone interview would be helpful in furthering the prosecution of this application, the Examiner is invited to contact the undersigned at the telephone number indicated below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952**. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: September 28, 1998

Respectfully submitted,

By: _____

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